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For Immediate Release

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Otsuka Announces Results of Phase 3 Data on Tolvaptan Under Development for ADPKD in U.S.

- Primary and key secondary endpoints were positive for tolvaptan vs. placebo in an additional Phase 3 clinical trial that examined the efficacy and safety of tolvaptan in autosomal dominant polycystic kidney disease (ADPKD)
- The data are intended to address the Complete Response Letter (CRL) issued by the FDA for a New Drug Application (NDA) for tolvaptan in ADPKD in 2013
- Trial results will be submitted for presentation at a nephrology medical congress in the second half of 2017

TOKYO, JAPAN – May 22, 2017 Otsuka Pharmaceutical Co., Ltd. announces positive top-line results from an additional Phase 3 clinical trial of tolvaptan in adult patients with ADPKD.

The primary endpoint of the trial was the change in estimated glomerular filtration rate (eGFR) from pre-treatment baseline levels to post-treatment assessment. In patients treated with tolvaptan the reduction in eGFR was significantly less than in patients treated with placebo ($p<0.0001$). eGFR is an estimate of the sum of the filtration rates of all single functional nephrons (filtering units) in the kidneys, measured through creatinine-based estimation equations.[1] The difference observed in this study represents a 35% reduction in the loss of kidney function compared to placebo in these patients over the course of one year. The key secondary endpoint was a comparison of the efficacy of tolvaptan treatment versus placebo in reducing the decline of annualized eGFR slope across all measured time points in the study. These data also showed significant benefit from tolvaptan vs. placebo ($p<0.0001$).

The trial was completed to supply confirmatory data to the previous study[2] to address the Complete Response Letter (CRL) issued by the U.S. Food and Drug Administration (FDA) in 2013 for a New Drug Application (NDA) for tolvaptan in the treatment of adults with ADPKD.

The Phase 3, multicenter, international, randomized-withdrawal, placebo-controlled, double-blind trial compared the efficacy and safety of tolvaptan (45 to 120 mg/day) to placebo. Trial enrollees were adults 18 to 65 years of age with ADPKD-induced chronic kidney disease between late stage 2 to early stage 4 (eGFR ranging from 65-25 mL/min) and not previously treated with tolvaptan. A total of 1,370 patients were randomized to either tolvaptan or placebo and were treated for a period of 12 months.[3]

There were no new safety issues identified for tolvaptan during the trial. As in the prior study,[2] tolvaptan resulted in more patients than placebo with increased (>3x upper limit of normal) levels of liver enzymes alanine aminotransferase (ALT; 5.6% vs. 1.2%) and aspartate aminotransferase (AST; 3.5% vs. 0.9%);

however, none of these patients exhibited total bilirubin greater than 2x ULN. The most common adverse events associated with tolvaptan (incidence >5% and at least 1% more frequent than placebo) included diarrhea (6.9% vs. 3.4%), fatigue (6.8% vs 3.5%) and polyuria (5.3% vs. 1.6%).

Results from the trial will be submitted for presentation at a nephrology medical congress in the second half of 2017.

About Tolvaptan and ADPKD

Tolvaptan is a selective vasopressin V_2-receptor antagonist. By selectively blocking vasopressin at the V_2-receptor, tolvaptan has been shown to decrease cyst-cell proliferation and fluid secretion, ultimately reducing cyst development.[4] In a previous Phase 3 clinical trial, tolvaptan was associated with reduced kidney growth and slowed decline of kidney function.[2]

ADPKD, a multi-systemic disease that is caused by inherited or acquired genetic mutation(s), is characterized by the formation and enlargement of cysts.[5] Cyst growth and proliferation eventually lead to kidney damage, and often cause complications that include pain and hypertension.[6,7] Up to 50% of patients require renal replacement therapy by the age of 60.[6] In addition to the physical effects, ADPKD causes psychological and emotional burden for those living with the disease and their loved ones.[8]

Tolvaptan is approved for the treatment of adult patients with ADPKD in Japan, the EU and other countries (see local prescribing information for specific indications in each country).

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